DETAILED ACTION

This action is in response to the amendment, filed 7/29/2009, in which claims 19-21 and 71-73 were canceled, claims 22, 24, 69, 70, 74-82 and 84-86 were amended, and claim 87 was newly added. Claims 22-70 and 74-87 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II and the species of first domain that is an artificial zinc finger protein (AZP) and second domain that is a GCL protein without traverse in the reply filed on 12/5/2007.

The restriction between Groups I and II was withdrawn in the Office action mailed 4/13/2009.

Claims 25 and 28-68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/5/2007.

Claim 83 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/5/2007. Applicant elected GCL as the second domain. The specification teaches that mouse germ-cell-less (GCL) protein binds LAP2β (e.g.,

page 2, lines 4-6). Thus, GCL is a lamina-binding protein, and claim 83 does not read on this species.

Currently, claims 22-24, 26, 27, 69, 70, 74-82 and 84-87 are under consideration.

Priority

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the

required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

It the instant case, the oath or declaration contains a claim for foreign priority to 60/351,315 and 60/350,163, which are US provisional application numbers. The first sentence of the specification does not contain a claim the benefit of the provisional applications under 35 USC 119(e). No ADS has been filed in the instant application.

Claim Objections

Claim 69 is objected to because of the following informalities: the claim should be amended to indicate that the one or more first domains further comprise one or a combination of the recited domains. Claim 69 depends from claim 22. In the reply filed 7/29/2009 claim 22 was amended to require the first domain to comprise a zinc finger protein of SEQ ID NO: 3. Claims 70 and 76-78 depend from claim 69 and are objected to for the same reason applied to claim 69. Appropriate correction is required.

Response to Arguments - Claim Objections

The previous objections of claims 69-82 and 84-86 have been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/29/2009.

Response to Arguments - 35 USC § 101

The rejection of claim 24 under 35 USC § 101 has been withdrawn in view of Applicant's amendment to the claim in the reply filed 7/29/2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-24, 26, 27, 69, 70, 74-82 and 84-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in the Office action mailed 4/13/2009 and has been rewritten to address the amendments to the claims in the reply filed 7/29/2009.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 22 is drawn to a nucleic acid comprising a nucleotide sequence encoding a chimeric protein comprising one or more first domains comprising SEQ ID NO: 3, capable of specifically binding a nucleotide sequence associated with a target gene, and one or more second domains capable of associating with the nuclear periphery, wherein at least one of said first domains is heterologous with respect to at least one of said second domains. Claim 23 is drawn to an expression vector comprising the nucleic acid of claim 22. Claim 24 is drawn to a host cell comprising the expression vector of claim 23. Claim 26 requires the expression vector of claim 23 to be a eukaryotic expression vector adapted for transfection into a cell containing a target gene for regulation. Claim 69 limits the one or more first domains encoded by the nucleic acid molecule of claim 22 to a zinc finger protein (ZFP) or an artificial zinc finger protein (AZP) (elected species). Claims 70 and 74 further limit the sequence of the zinc finger proteins encoded by the nucleic acid. Claims 76-78 are directed to the number of zinc fingers present in the protein encoded by the nucleic acid. Claim 79 limits the one or more

second domains encoded by the nucleic acid molecule of claim 22 to domains that directly or indirectly associate with or bind to the nuclear envelope, the nuclear lamina, heterochromatin, or any combination thereof. The elected species of second domain, germ-cell-less (GCL) protein binds LAP2β, a lamina-associated protein. Claim 80 specifically requires the second domain to comprise a GCL protein or binding moiety of a GCL protein. Claim 81 limits the one or more second domains encoded by the nucleic acid molecule of claim 22 to a nuclear envelope-binding protein, a nuclear lamina-binding protein (reads on elected species), a heterochromatin protein or a protein capable of associating with or binding to any one of said proteins or combination thereof. Claim 82 limits the one or more second binding domains to a lamina-binding protein (reads on elected species). Claim 84 limits the nucleic acid of claim 22 to one that encodes from one to six first domains and from one to six second domains. Claim 85 further requires the nucleic acid molecule of claim 22 to encode a nuclear-localization signal, and claim 86 requires the nucleic acid molecule of claim 22 to encode a cellular uptake signal. Claim 87 requires the target gene bound by the DNA binding domain to comprise a sequence elected from the group consisting of SEQ ID NOs: 6-8. The nature of the invention is complex in that one must know how to use the protein encoded by the nucleic acid molecule, where the encoded protein is a chimeric protein of at least two heterologous portions that have two different functions.

Claim 27 is drawn to a pharmaceutical composition comprising a therapeutically effective amount of the nucleic acid or expression vector of claim 22 in admixture with a pharmaceutically acceptable carrier. The nature of the invention is complex in that the nucleic acid molecule must be capable of treating a disease in a subject to which it is administered. Thus, one must know how to make and use the nucleic acid molecule to treat disease.

Breadth of the claims: The claims are specifically drawn to nucleic acid molecules comprising a nucleotide sequence that encodes a chimeric protein comprising one or more first domains capable of specifically binding a nucleotide sequence associated with a target gene and one or more second domains capable of associating with the nuclear periphery. However, the claims are incredibly broad with respect to the specific structure of the one or more first domains and one or more second domains. The claims encompass a sequence encoding any protein structure that specifically binds a nucleotide sequence. Some structural limitations are provided in the dependent claims reciting a zinc finger or a particular genus of zinc finger domains to be present in the protein encoded by the nucleic acid. However, these sequences are broadly defined such that they could essentially bind to any target sequence located in a target region of any cell. The claims also encompass a sequence encoding any domain capable of associating with the nuclear periphery by directly or indirectly associating with or binding to the nuclear envelope, nuclear lamina, heterochromatin, or any combination thereof. Claim 80 is directed to a sequence encoding GCL protein or a binding moiety of GCL protein; however this claim reads on a sequence comprising any first domain capable of specifically binding a nucleotide sequence associated with a target gene. With respect to claim 27, the claim broadly reads on a pharmaceutical composition for the treatment of any disease by targeting any gene in any eukaryotic organism. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions the use of the chimeric proteins encoded by the claimed nucleic acid molecules to repress or down-regulate expression of selected target genes (e.g., page 1, lines 5-10). The

specification notes that genes found in heterochromatin are tanscriptionally silent (e.g., page 1, lines 16-18). Heterochromatin appears to be associated with the nuclear periphery in eukaryotes (e.g., page 1, lines 18-20). Based upon this observation, the specification suggests that bringing genes into proximity with heterochromatin or the nuclear periphery may play a role, at least in part, in gene silencing. The disclosed invention is based upon this hypothesis. Specifically, the specification envisions using a sequence-specific DNA binding domain to bring a gene into association with the nuclear periphery to silence or down regulate (repress) expression of that a target gene (e.g., page 2, lines 13-16).

The nuclear periphery of higher eukaryotes (metazoans and above) consists of a nuclear envelope (NE) with inner and outer membranes and a nuclear lamina (e.g., page 1, lines 24-25). The nuclear lamina is composed of intermediate filaments termed lamins and lamina-associated proteins (LAPs), and some LAPs are also integral membrane proteins of the inner nuclear membrane (e.g., page 1, lines 26-29). The specification notes a few prior art examples where a naturally occurring protein represses transcription when associated with the nuclear periphery, including Oct-1, retinoblastoma protein (Rb), and germ-cell-less protein (GCL) (e.g., paragraph bridging pages 1-2).

The specification envisions using the chimeric protein encoded by the claimed nucleic acid molecules to down regulate expression of a target gene from a target sequence in a plant gene, a mammalian gene, an insect gene, a yeast gene or from a virus such as a DNA virus (e.g., page 4, lines 15-18). When the target gene or site is from a mammal, the specification envisions targeting the expression of a cytokine, an interleukin, an oncogene, an anti-angiogenesis factor, a drug resistance gene and/or any other desired target (e.g., page 4, lines 18-24). The specification

envisions down regulating genes to down regulate or shut off genes involved in oncogenesis, cellular proliferation and regeneration, angiogenesis (when unwanted blood vessel formation occurs such as in tumors), to control particular stages of development or growth in plants, or to down regulate or shut off viral genes (e.g., page 7, lines 4-16; page 19, line 6 to page 20, line 2).

With respect to the first domain of the encoded chimeric protein, the specification teaches that zinc finger proteins (ZFP) are well-known DNA binding proteins that recognize and bind to target DNA sequences by interaction of the target sequence with particular amino acids in the alpha helix of each zinc finger (e.g., paragraph bridging pages 2-3). Specifically, the Cys_2-His_2 class of ZFPs have been extensively studies and permit the design of artificial zinc finger proteins (AZPs) that bind predetermined DNA target sequences (e.g., paragraph bridging pages 2-3). A number of different DNA binding proteins are known in the art and are known to function to bind DNA in a sequence specific manner (e.g., pages 8-15). Known transcriptional repressor proteins include a DNA binding domain and a transcriptional repression domain, such as the repression domain from human KOX-I protein (e.g., paragraph bridging pages 15-16).

With respect to the second domain of the encoded chimeric protein, the specification envisions the use of nuclear envelope and/or nuclear lamina-binding proteins, including lamins (e.g., lamins A, B and C), lamina-binding proteins (such as LAP 2β), and GCL, which appears to bind indirectly to the nuclear lamina via lamina-associated protein (LAP) (e.g., paragraph bridging pages 16-17). The specification also envisions using the hyperphoshporylated from of Rb, Oct-1, the insulin activator IPF/PDX-1, HP1, and polycomb group proteins (e.g., paragraph bridging pages 16-17).

Guidance is provided with respect to the inclusion of a nuclear localization sequence (e.g., page 17, lines 13-19), a cellular uptake signal (e.g., page 17, line 20 to page 18, line 21), and the construction of expression vectors (e.g., pages 23-29). The section title "Pharmaceutical Formulations" provides general guidance on the formulation of nucleic acid molecules but does not provide specific guidance on the formulation of nucleic acid molecules comprising specific nucleic acid sequences for targeting specific genes to induce a particular therapeutic effect (e.g., pages 36-37).

The specification does not contain any working examples that teach the use of the claimed nucleic acid molecules, or proteins encoded thereby. The specification sets forth a prophetic example, Example 1, titled "Repression of human VEGF-A." The example discloses two AZPs targeted to two different sequences (SEQ ID NOs: 7 and 8) of the human vascular endothelial growth factor A (VEGF-A) gene. The specification envisions fusing each AZP to more GCL protein to make CP1-vegf and CP2-vegf. The specification discloses how to test for repression activity in a human histiocytic lymphoma cell line but does not disclose the results of such an assay.

Predictability and state of the art: The state of the art was underdeveloped as of the effective filing date of present application. The specification discloses that the intended use of the claimed nucleic acid molecules is to produce chimeric proteins capable of down regulating, repressing or shutting off transcription by a mechanism involving the binding of a DNA binding domain to a target sequence in a gene and the localization of the chimeric protein and bound gene to the nuclear periphery, where localization is driven by the second protein domain of the chimeric protein. As discussed above, no working examples are provided in the present

specification. There is no prior art of record that teaches the regulation of the transcription of a gene by localizing the gene to the nuclear periphery as an art-accepted phenomenon. The specification teaches that the nuclear periphery includes the nuclear envelope and the nuclear lamina, and a gene in proximity to the nuclear periphery is physically adjacent to the nuclear periphery (e.g., page 7, lines 17-22). While Stein et al (US Patent No. 6,153,729, cited as reference 1 on the IDS filed 11/12/2004) teach the localization of a protein to the nuclear matrix using a nuclear matrix targeting peptide (e.g., column 20, lines 14-44), the localization to the nuclear matrix cannot be equated with localization to the nuclear periphery. Nickerson et al (Proc. Natl. Acad. Sci. USA, Vol. 94, pages 4446-4450, April 1997) teach that the nuclear matrix consists of two parts: the nuclear lamina and a network of intricately structured fibers connected to the lamina and well distributed through the nuclear volume (e.g., Figure 3). Furthermore, the references of record that teach localization to the nuclear matrix can have variable results on gene expression (WO 00/28054, cited as reference 1 on the IDS filed 6/2/2006; e.g., page 2, lines 23-36). The underdeveloped nature of the present invention is further evidenced by the post-filing art. Reddy et al (Nature, Vol. 452, No. 7184, pages 243-247, March 2008) teach that the ability of the nuclear periphery to regulate gene activity has not been functionally tested in metazoan cells (e.g., page 243, left column, last full paragraph). While Reddy et al were able to demonstrate the repression of a transgene integrated into the genome of a eukaryotic cell by expressing a fusion protein comprising a LacI DNA binding domain and a EMD protein fragment that is capable of localizing to the nuclear membrane (e.g., e.g., page 243, paragraph bridging columns; page 245, paragraph bridging columns), these results were not reproducible in the system used in a study by Kumaran et al (The Journal of Cell Biology, Vol. 180, No. 1, pages

51-65, January 2008). Kumaran et al teach the targeting of a genetic locus to the nuclear lamina using a fusion protein comprising a LacI DNA binding domain and a lamin B1 protein in a cell that contains an integrated transgene comprising Lac operator repeats (e.g., page 52, paragraph bridging columns; page 53, paragraph bridging columns; Figure 1). Contrary to the results obtained by Reddy et al, Kumaran et al teach that the localization of the genetic locus to the nuclear periphery did not affect the expression of the gene even though the locus appeared as a flattened signal plastered against the nuclear periphery (e.g., page 54, left column; page 61, paragraph bridging columns). Further, Finlan et al (PLoS Genetics, Vol. 4, No. 3, e1000039, pages 1-13, March 2008) teach that a chimeric fusion protein comprising LacI and Lap2β is able to repress some genes but allows some genes to remain transcriptionally active (e.g., paragraph bridging pages 1-2; page 2, Author Summary). Kumaran et al teach that the broad morphological classification of chromatin into euchromatin and heterochromatin does not always correlate with gene activity (e.g., page 51, right column, full paragraph). Accordingly, the effect of localizing a gene to the nuclear periphery is unpredictable. Ruault et al (Trends in Genetics, Vol. 24, No. 11, pages 574-581, September 2008) teach that the impact of the lamina association on gene expression can vary depending on the nature of the genes, their promoters and their chromatin environment before the tethering event (e.g., page 578, left column, 1st full paragraph).

While the post-filing art asserts that a few proteins were known to silence transcription by localization of genes to the nuclear periphery in yeast (Finlan et al. (2008), e.g., page 1, paragraph bridging columns; Ruault et al (2008), e.g., page 575, right column). Tham et al (Molecular Cell Vol. 8, pages 189-199, July 2001) teach that it is not clear whether telomere

localization to the nuclear periphery in yeast is the cause or consequence of transcriptional silencing (e.g., paragraph bridging pages 189-190). Moreover, Finlan et al and Ruault et al teach that the results observed in yeast cannot be reproduced in a predictable manner in mammalian cells due to the increased complexity and underdeveloped state of the art in this area (e.g., Finlan et al (2008), e.g., page 1, paragraph bridging columns; Ruault et al (2008), e.g., paragraph bridging pages 575-576; Table 1; page 578. left column, 1st full paragraph). As noted by Finlan et al, yeast do not appear to have the extensive array of integral membrane proteins and lamins that are present at the periphery of the mammalian nucleus (e.g., page 1, paragraph bridging columns).

Given the unpredictability of the effect of localizing a gene to the nuclear periphery, it would be unpredictable to deliver a nucleic acid molecule encoding a chimeric protein for the treatment of a disease. Claim 27 requires the composition to comprise a "therapeutically effective amount" of the nucleic acid molecule. Furthermore, at the time the invention was made, it was not routine in the art to use nucleic acid molecules for therapeutic applications. An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al (1997) indicate that most approaches suffer from poor efficiency and transient expression of the gene

(e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). The post filing art indicates that gene therapy methods still suffer from inefficient gene transfer (Verma and Weitzman, Gene Therapy: Twenty-first century medicine. Annual Review of Biochemistry, Vol. 74, pages 711-738, 2005; e.g. page 712, last paragraph). Regarding viral methods for gene delivery *in vivo*, Verma et al (1997), indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Gene therapy is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique (e.g. Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al, p. 33, col. 1, 1st paragraph; Verma and Weitzman, page 732, 2nd full paragraph).

Amount of experimentation necessary: Because enablement of the claimed invention is based upon localization of a gene to the nuclear periphery resulting in a predictable down regulation of transcription, and because the post-filing art teaches that the regulation of genes localized to the nuclear periphery is unpredictable, the use of any nucleic acid molecule that falls within the scope of what is claimed would be unpredictable. For each nucleic acid encoding a chimeric protein, one would be required to express the protein in a eukaryotic cell and measure the expression of the gene bound by the DNA binding domain of the transcription factor. The effect of the altered localization of the gene must be empirically determined.

With respect to the claimed pharmaceutical composition, the quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how make and use the claimed composition for therapy. With any nucleic acid one would have to determine how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 22-24, 26, 27, 69, 70, 74-82 and 84-87 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

The rejection of claims 19-21 under 35 U.S.C. 112, second paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 7/29/2009.

The rejection of claims 71-73 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 7/29/2009.

With respect to the rejection of claims 22-24, 26, 27, 69, 70, 74-82 and 84-87, Applicant's arguments filed 7/29/2009 have been fully considered but they are not persuasive.

The response notes that claim 22 has been amended. The response asserts that the claim has been amended to one sequence, such that one skilled in the art could use SEQ ID NO: 3 to target a gene or genetic sequence to reduce its expression.

Applicant's summary of the claimed subject matter is not consistent with the claimed invention. Claim 22 recites, "A nucleic acid molecule comprising a nucleotide sequence encoding a chimeric protein comprising one or more first domains comprising SEQ ID NO: 3, capable of specifically binding a nucleotide sequence associated with a target gene and one or more second domains capable of associating with the nuclear periphery, wherein at least one of said first domains is heterologous with respect to at least one of said second domains." First, SEQ ID NO: 3 is not limited to one sequence. SEQ ID NO: 3 is the following: Pro-Tyr-Lys-Cys-Pro-Glu-Cys-Gly-Lys-Ser-Phe-Ser-Z^{-1}-Ser-Z^2-Z^3-Leu-Gln-Z^6-His-Gln-Arg-Thr-His-Thr-Gly-Glu-Lys, where Z^{-1} is Arg, Lys, Gln, Asn, Thr, Met, Leu, Ile, Glu or Asp, Z^2 is Ser, Art, Asn, Gln, Thr, Val, Ala, Asp or Glu, Z^3 is His, Lys, Asn, Gln, Ser, Ala, Val, Thr, Asp or Glu, and Z^6 is Arg, Lys, Gln, Asn, Thr, Tyr, Leu, Ile, Met, Glu or Asp. Second, the sequence of SEQ ID NO: 3 only comprises one domain encoded by the nucleic acid molecule of claim 22. The claim also requires the nucleic acid to encode a second domain of any protein capable of associating with the nuclear periphery, where this domain is of any sequence. The specification envisions using the proteins encoded by the nucleic acid molecule to repress transcription by brining a gene bound by the first domain to the nuclear periphery; however, the art teaches that localization of a gene to the nuclear periphery has unpredictable effects on gene expression (see pages 13-17 of the Office action mailed 4/13/2009). Applicant has not provided evidence that

any protein encoded by the claimed nucleic acid molecules could be used to repress gene expression of the target gene.

The response asserts that it was elementary in the art, at the time of filing, to encode and synthesize such a molecule as described in the claims.

This argument is not found persuasive. While it was within the skill of the art to synthesize nucleic acid molecules and proteins, one would not know how to use the encoded proteins. Due to the unpredictable nature of the invention, the function of each of the encoded proteins would have to be empirically determined. To test each protein for a function would require undue experimentation.

The response asserts that the specification teaches several nuclear periphery domains that would enable one skilled in the art to choose the one most appropriate to the purpose. Further, the response asserts that several linking peptides are described that would further teach one skilled in the art appropriate sequences for which to encode n the claimed nucleic acid molecule.

These arguments are not found persuasive. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the

invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). In the instant case, one would have little or no knowledge based upon the teachings of the prior art and specification with regard to how to use the encoded proteins. The art of record indicates that the level of unpredictability of the invention is high, and the specification does not provide specific guidance with regard to nucleic acid molecules that encode particular proteins with the ability to repress transcription of a target gene by bringing the gene in contact with the nuclear periphery.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Arguments - 35 USC § 102

The rejection of claims 22-24, 26, 69 and 84 under 35 U.S.C. 102(b) as being anticipated by Andrulis et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/29/2009. Andrulis et al do not teach a nucleic acid molecule comprising SEQ ID NO: 3 as now claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston
Examiner
Art Unit 1636

/JD/

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636